# Sample size calculations for comparing rate of decline

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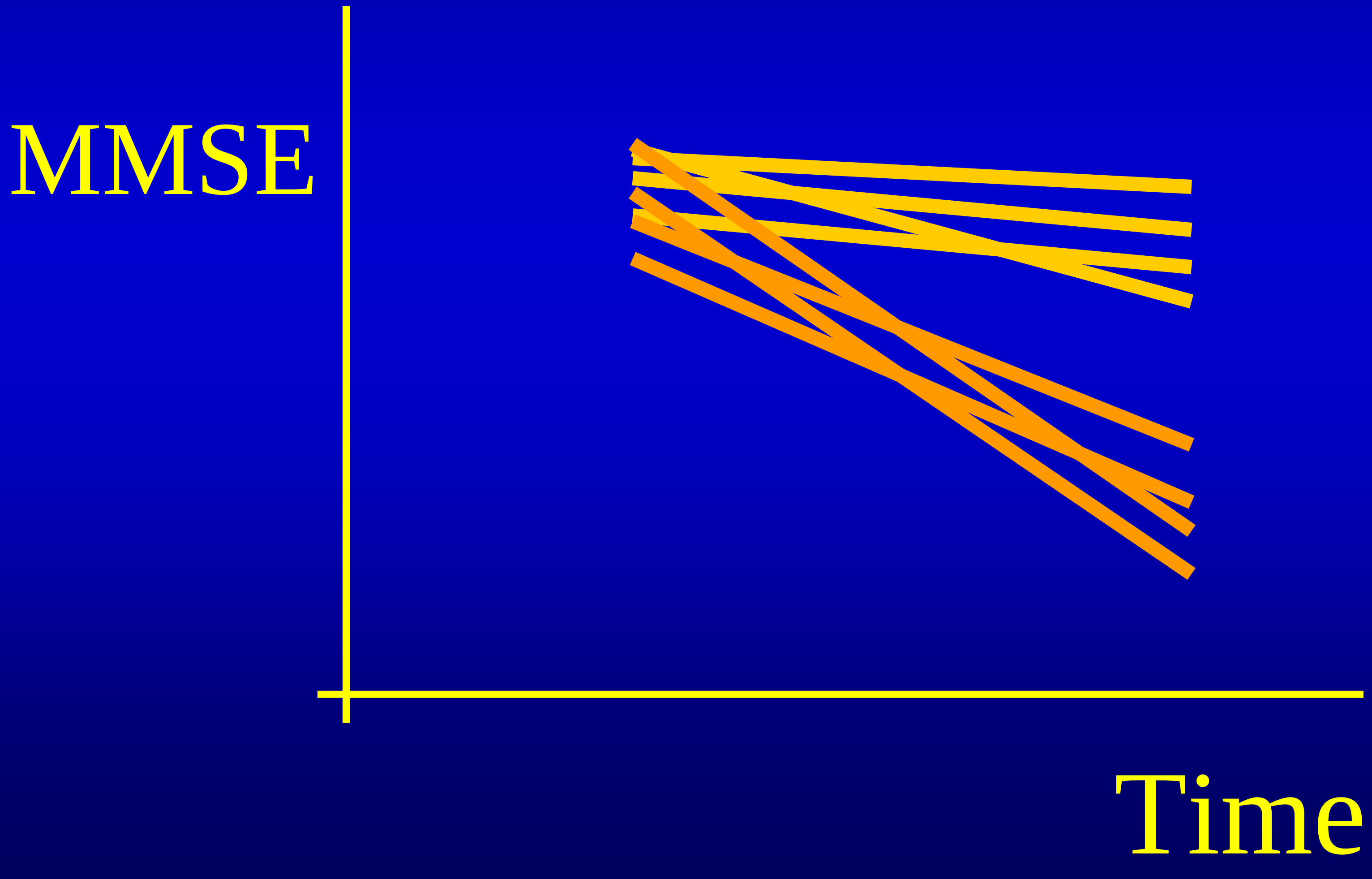
# E.g., use ADC data to power rate of decline analysis for:

- cohort studies
- clinical trials
- grants to analyze existing data (NACC proposals)

# E.g., AD treatment trial

## Outcome: MMSE



# E.g., Cohort Study (Wilson, Bennett et al. Neuroepidemiology 2006;26:61-67)

**Table 2.** Relation of odor identification score to baseline level of function and annual rate of change in different cognitive domains

| Cognitive domain | Model term | Estimate (SE) | p value |
|---|---|---|---|
| Perceptual speed | Time | –0.071 (0.016) | <0.001 |
| | Odor identification | 0.089 (0.016) | <0.001 |
| | Odor × time | 0.015 (0.006) | 0.013 |
| Episodic memory | Time | –0.045 (0.016) | 0.004 |
| | Odor identification | 0.085 (0.012) | <0.001 |
| | Odor × time | 0.012 (0.006) | 0.030 |
| Semantic memory | Time | –0.056 (0.014) | <0.001 |
| | Odor identification | 0.081 (0.011) | <0.001 |
| | Odor × time | 0.007 (0.005) | 0.156 |
| Working memory | Time | –0.049 (0.019) | 0.009 |
| | Odor identification | 0.074 (0.014) | <0.001 |
| | Odor × time | 0.012 (0.007) | 0.084 |
| Visuospatial ability | Time | –0.007 (0.022) | 0.751 |
| | Odor identification | 0.059 (0.014) | <0.001 |
| | Odor × time | –0.003 (0.008) | 0.667 |

Estimates are from mixed-effects models adjusted for age, sex, and education and indicate the effect of a 1-point change in odor identification score.

# Possible Analytic Methods

- Least Squares ‘Summary Measure’
- Random Effects Model / reml
- Marginal Model / gee

# Least Squares 'Summary Measure'

- aka the NIH method
- aka 'two-stage' analysis
- Cook and Ware: "we recommend this two-stage analysis both for its efficiency and ease of interpretation." (*Annual Review of Public Health.* 1983; 4:1-23)

# Least Squares ‘Summary Measure’

- Esp. good for prevalent case data
  - less prone to spurious findings (Milliken & Edland, SIM 2000)
  - useful for describing relationship between stage of disease and rate of decline (e.g. Morris, Edland et al. Neurol 1995)
- Power using t-test formula (Schlesselman, 1971)

# Power Formulas

- Random Effects Model / reml
- Marginal Model / gee

# Power formula - RE model

*(Hartley and Rao Biometrics;1966)

$$N/Arm = 2[X'V^{-1}X]_{2,2}^{-1}(z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$$

*where*

- $X = (\mathbf{1}, \mathbf{t})$ = *the design matrix*
- $V = Var(Y)$
- $\Delta$ = detectable effect size

  = detectable difference in mean rate of decline
- balanced data, *Var(Y)* assumed known

# Power formula - gee

*(Liu and Liang Biometrics;1997)

$$N/Arm \sim 2[X'V^{-1}X]_{2,2}^{-1}(z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$$

*where*

- $X = (\mathbf{1}, \mathbf{t})$ = *the design matrix*
- $V = Var(Y)$
- $\Delta$ = detectable effect size

  = detectable difference in mean rate of decline
- balanced data, *Var(Y)* assumed known

# *Choices described for *Var(Y)*:

1) unstructured

2) of form $\sigma^2 R$, $R = Cor(Y)$

- compound symmetry
- autoregressive

*Liu and Liang Biometrics (1997); see also Rochon SIM (1998), Jung and Ahn SIM (2003), and others

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# Note:

$Var(Y) = \sigma^2 R$ implies parallel line trajectories

AD trajectories fan apart

# Simulation study:

Power using AD pilot data and compound sym. assumption (ADAS-cog, $\Delta$=1.2, power = 80% and 90%)

Simulate true power (given slopes fan apart)

| Nominal power | (Sample Size) | Observed Power |
|---|---|---|
| 80% | (m=104) | 24% |
| 90% | (m=139) | 30% |

Therefore,

Use $V = Var(Y)$ implied by model with random intercepts *and* random slopes:

$$N/\text{Arm} = 2[X'V^{-1}X]_{2,2}^{-1}(z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$$

$$V = V(Y_i) = Var(\alpha_i + \beta_i t_{ij} + \varepsilon_{ij}) = \ldots$$

$$V^{-1} = \ldots$$

$$[X'V^{-1}X]^{-1} = \ldots$$

$$N/Arm = \ldots$$

$$N/Arm = 2\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$$

where

$$\sigma^2 = \sigma_\beta^2 + \sigma_\varepsilon^2/\Sigma(t - t.)^2$$

$$N/Arm = 2\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$$

where

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Variance of random slopes

$$N/Arm = 2\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$$

where

$$\sigma^2 = \sigma_\beta{}^2 + \sigma_\varepsilon{}^2 / \Sigma(t - t.)^2$$

Residual error variance

$$N/Arm = 2\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$$

where

$$\sigma^2 = \sigma_\beta^2 + \sigma_\varepsilon^2 / \Sigma(t - t.)^2$$

Estimable by random effects model fit to pilot data

# sample pilot data model fit

```
>lme(y~time, random = ~time|id)

Linear mixed-effects model fit by REML

Random effects:
 Formula: ~time | id

            StdDev   Corr
(Intercept) 5.575794 (Intr)
time        2.382019 0.158
Residual    3.028220

Fixed effects: y ~ time
                Value Std.Error  DF   t-value
(Intercept) 16.706180 0.5945337 599 28.099634
time         1.637609 0.2642732 599  6.196652
```

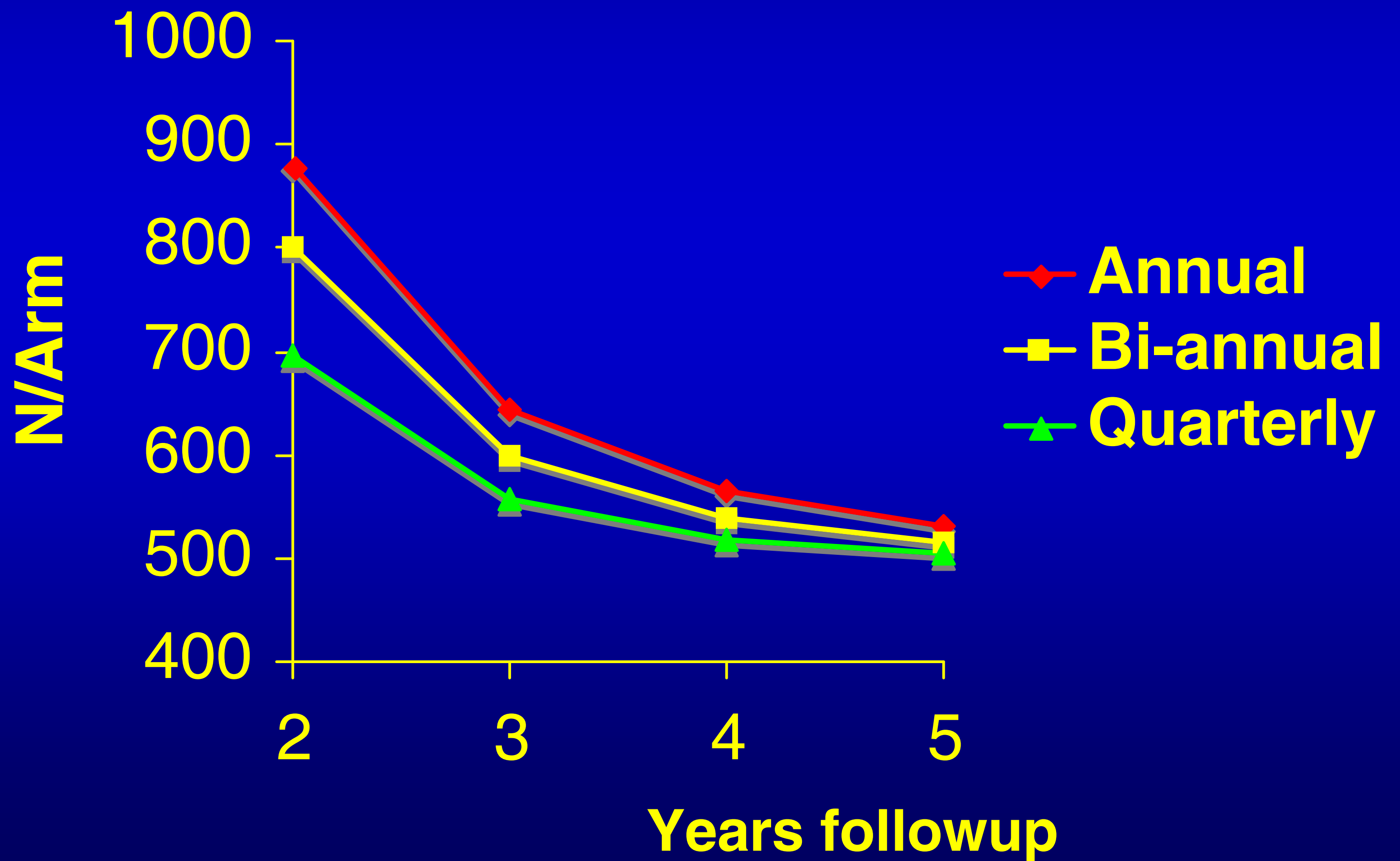
$$N/Arm = 2\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$$

where

$$\sigma^2 = \sigma_\beta^{\,2} + \sigma_\varepsilon^{\,2}/\Sigma(t - t.)^2$$

Determined by Study Design

# N/Arm as a function of design
## (Alzheimer's treatment trial, outcome = ADAS-cog, effect size = 33% reduction in mean slope)



$$N/Arm = 2\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$$

where

$$\sigma^2 = \underline{\sigma_\beta}^2 + \underline{\sigma_\varepsilon}^2 / \Sigma(t - t.)^2$$

Varies by Instrument

# Sample Size, ***Prevention Trial*** with Biannual Sampling, 2 or 3 Year Followup, 6 Month Sampling Interval, Effect Size = 50% Reduction in Mean Slope, Power = 90%

| | Mean Slope | $\sigma_\beta$ | $\sigma_\varepsilon$ | N/Arm | |
|---|---|---|---|---|---|
| | | | | 2Yr | 3Yr |
| Word List Delayed Rec. | -.17 | 0.20 | 1.27 | 1985 | 784 |
| WMSR LM I | .73 | 1.18 | 2.44 | 595 | 354 |
| WMSR LM II | .89 | 1.20 | 2.48 | 415 | 247 |

(Pilot data courtesy OHSU ADC, Jeffery Kaye Director)

# Caveats

- **increase N to account for expected dropout rate**
- **Pilot data should be representative of study population (else, see Liu and Liang 1977 for covariate weighted power formula)**

# Conclusions: 1

- **Sample size can be dramatically underestimated when the compound symmetric model is used**

- **E.g., Alzheimer treatment trial setting:**
  - **Nominal power = 90%**
  - **Actual power = 30%**

# Conclusions: 2

**The covariance structure implied by a random intercepts, random slopes model:**

- **is more consistent with typical longitudinal data**
- **can be expressed in terms of $\sigma_\beta^2$ and $\sigma_\varepsilon^2$ (easily estimated from pilot data)**
- **leads to heuristically appealing power formula**